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(54) Title: POROUS NICKEL-TITANIUM STRUCTURE USED AS A CARRIER FOR LIVING CELLS

(57) Abstract: A carrier device for an artificial internal organ has a matrix of porous nickel titanium alloy, the porosity of the matrix being effective to isolate cells of the desired internal organ in the matrix, from immune system entities, for example macrophages. The matrix is, in particular, derived from a powder composition composed of 45 to 55 %, by weight, of nickel powder and 55 to 45 %, by weight, titanium powder, to a total of 100 %; and titanium nickel alloy powder in an amount of 5 to 30 %, by weight, based on the total weight of nickel and titanium powders.

POROUS NICKEL-TITANIUM STRUCTURE USED AS A CARRIER FOR LIVING CELLS

TECHNICAL FIELD

This invention relates to a medical device which forms the matrix of an artificial internal organ and to manufacture of such a device.

BACKGROUND ART

A crucial new method for the radical treatment of diseases of the internal organs is the partial or total substitution of their functions by the transplantation of a corresponding artificial organ prepared according to modern technologies. The resolution of the central problem - the suppression of the recipient's immune response to the artificial organ has resulted in remarkable progress in this area of medicine. One of the most effective methods is the isolation of the transplanted cells by placing them into a porous matrix. (*Medical Materials and implants with Shape Memory*, Tomsk: Tomsk University, 1998, p. 355.) The essence of this method is the isolation of the smaller implanted cells from larger immune system entities such as macrophages based on the size difference. The task is therefore to create a matrix with the required distribution of pore sizes to isolate the desired cells in the matrix.

In nature there is no gradated transformation of any process or relationship; this also applies to the pore size distribution within the porous material. It is in principle difficult to create a porous material that would strictly exclude pores of a certain pre-defined size.

Owing to its bio-compatibility, nickel-titanium alloy or nickelide of titanium is the most effective material for the manufacture of a matrix for cellular-suspensions in the formation of an artificial internal organ. Its porous structure is created during the SHS (self-propagating high-temperature synthesis) process within a blank of a predetermined shape

made of the alloy. The fundamentals of this technology are based on the utilization of the heat which is emitted during the exothermic interaction of the heterogeneous metals, nickel and titanium. Following the thermal excitation of a certain local volume, the emitted heat of the interaction heats up the adjacent layers of the blank, thus ensuring the self-propagation of the reaction.

It is known to manufacture porous alloys of nickelide titanium by means of SHS employing an alloy containing powders of nickel and titanium, in certain cases with some alloying addition as in G. T. Dambaev, V. E. Gunter, et al, *Porous Permeable Superelastic Implants in Surgery,* Tomsk: Russian Medical and Engineering Centre, Siberian State Medical University, 1996, p. 35. The nickel and titanium powders are dried, weighed, mixed and molded by pressing them into the shape expedient for the future application. The resulting compact blanks are placed into a reactor, which is a container made of stainless steel with screwed covers, electrical current feeds, an electrical filament for the ignition of the powder mixture and inert gas-flow regulator, and thermocouple vents. The reactor is filled with inert gas, for example, argon, under a pressure of 1-2 at.

In order to initiate the exothermic reaction, the reactor is warmed externally, increasing the temperature in the ignition space to 423-623°C. The alloy is then ignited with the electrical filament. When the laminar or layer by layer self-heating process and the sintering of the nickel and titanium powders has been completed, the reactor is cooled without termination of the inert gas supply and the synthesized porous matrices are extracted from the reactor.

This alloy and the related technology are widely used in modern medicine, especially in areas where there are no strict requirements for the distribution of the porosity. The disadvantage of this technology for the

manufacture of material for cellular-suspension matrices is the high percentage of pores with a size exceeding the size of macrophages, due to the lack of control in the pore-formation process.

An existing alloy of nickel and titanium used for the production of the material based on nickelide titanium using the SHS method is described in USSR Inventor's Certificate No. 662270, Class B 22 F 3/12, *The Technique of Production of Materials Based on TiNi Alloy*, published 15.05.1979, Bulletin No. 18 (prototype). The SHS technology decreases the number of the larger pores in the prototype material by raising the preheating temperatures of the reactor containing the alloy of 0.5 - 0.9 of the fusing point of the final product. As a result, synthesis takes place in the liquid phase, thus providing a higher percentage of small-sized pores as well as a dense structure. The disadvantage of the prior technique is the insufficient control of pore-size distribution of the synthesized matrix.

DISCLOSURE OF THE INVENTION

The technical result of the present invention is the improved regulation of pore-size distribution during the process of self-propagating high-temperature synthesis in manufacturing porous material as a matrix for cellular suspensions.

In accordance with one aspect of the invention there is provided a carrier device for an artificial internal organ comprising a matrix of an intermetallic material based on the elements nickel and titanium, said matrix having a porosity effective to isolate organ cells in the matrix from immune system entities, for example macrophages.

In another aspect of the invention there is provided an artificial internal organ precursor comprising a carrier device of the invention, and organ cells isolated in the pores of the matrix.

In still another aspect of the invention there is provided an artificial internal organ comprising a carrier device of the invention, and an organ cell growth structure extending throughout the pores of the matrix.

In yet another aspect of the invention there is provided a method of producing a carrier device for an artificial internal organ comprising: forming a shaped pressed article simulating an artificial internal organ, of nickel and titanium powders and nickel titanium alloy powder, subjecting said pressed article to a self-propagating high temperature synthesis to produce nickel titanium alloy from said nickel and titanium powders with formation of a porous matrix corresponding to said shaped article, said porous matrix having a porosity effective to isolate organ cells in the matrix from immune system entities, for example macrophages.

In still another aspect of the invention there is provided a method of forming an artificial internal organ comprising: implanting a precursor of the invention in a recipient in need of an artificial internal organ, said cells being cells which form the needed organ and allowing cell growth to establish throughout the matrix.

In yet another aspect of the invention there is provided use of a carrier device of the invention for the formation of an artificial internal organ.

DESCRIPTION OF PREFERRED EMBODIMENTS

The carrier device of the invention serves to isolate within it, organ cells which will grow throughout the matrix of the device, from larger immune system entities such as macrophages which would otherwise attack the organ cells. The organ cells are isolated within the matrix and the immune system entities are unable to penetrate the matrix to attack the organ cells because of their larger size.

In particular embodiments, the matrix is derived from a powder composition composed of 45 to 55%, by weight, of nickel powder and 55 to 45%, by weight, titanium powder, to a total of 100%; and titanium nickel alloy powder in an amount of 5 to 30%, by weight, based on the total weight of nickel and titanium powders.

Preferably the powder composition contains 47 to 53%, by weight of said nickel powder and 53 to 47%, by weight of said titanium powder to a total of 100%.

Suitably at least 30%, and preferably at least 50%, of the porosity of the matrix is defined by pores having a pore size of less than 100 microns.

An analysis of the kinetics of the self-propagating high-temperature synthesis demonstrates complicated multifunctional relationships of the final structure of the synthesized intermetallic compound to the initial conditions of the synthesis: the proportions of the original components, the degree of their dispersion and compactness, the inert gas pressure and other factors. These parameters condition the propagation velocity of the combustion wave, the maximal temperature of the synthesis and the intensity of gas release. All of these attributes determine the final structure of the synthesized material in its variations from highly porous to dense.

The addition of TiNi powder, the inert element in the reaction, changes the SHS kinetics and provides the required pore-size distribution, so as to create a required porosity and to ensure the isolation of the cells of an artificial organ from macrophages; it was found that the proportion of the inert TiNi component should be 5-30%, by weight, based on the total weight of the mixture of nickel and titanium powders. When the percentage of the TiNi powder is less than 5%, the synthesis can not be efficiently controlled; when the percentage of the TiNi powder is higher than 30%, the synthesis does not take place.

An additional technical benefit of the proposed invention is the improvement of the mechanical workability of the synthesized material.

DESCRIPTION OF DRAWINGS

The invention is illustrated by reference to the drawings in which:

Fig. 1 is a photomicrograph of a conventional porous structure of TiNi alloy; and

Fig. 2 is a photomicrography of the porous structure of TiNi alloy in accordance with the invention.

EXAMPLE

The alloy used to produce the porous material contained a mixture of titanium (brand PTOM) and nickel (brand PNK-10T2) powders in a stoichiometric proportion, by weight, of 50:50 each, and TiNi powder in an amount of 15%, by weight, based on the total weight of the mixture of nickel and titanium powders.

The mixture obtained after 8 hours of blending in a laboratory blender was loaded into a cylindrical closed mould with a diameter of 30 mm and a length of 250 mm; the mould was placed into a reactor. A flow or argon was directed through the reactor to prevent the access of ambient air. The reactor was heated to a temperature of 600°C. and the formed alloy was ignited with the electrical filament. Self-propagating high-temperature synthesis developed in a layered regime of combustion and lasted for 15 seconds.

The technical result of the present solution becomes clear in a comparison of the structure of the synthesized porous material of the invention (Fig. 2) with the structure of the material obtained using similar technology in the prior art (Inventor's Certificate 662270). The percentage of pore sizes ranging from 0 to 100 microns was evaluated in both samples. In the prior art of Fig. 1, 5% of the pores were of this size, the remainder of

the pores being larger; in the present technical solution, 50% of the pores were of this size. Visual evaluation gave evidence of an abrupt decrease in pore-sizes ranging from microns to fractions of a micron. The material synthesized using the present technology was successfully employed in a clinical trial in treatment of parenchymatous organs involving their partial or total substitution by transplants.

CLAIMS

1. A carrier device for an artificial internal organ comprising a matrix of an intermetallic material based on the elements nickel and titanium; said matrix having a porosity effective to isolate organ cells in the matrix from immune system entities.

2. A carrier device according to claim 1, wherein said intermetallic material is derived from a powder composition composed of 45 to 55%, by weight, of nickel powder and 55 to 45%, by weight, titanium powder, to a total of 100%; and titanium nickel alloy powder in an amount of 5 to 30%, by weight, based on the total weight of nickel and titanium powders.

3. A carrier device according to claim 2, wherein said powder composition contains 47 to 53%, by weight of said nickel powder; and 53 to 47%, by weight of said titanium powder to a total of 100%.

4. An artificial internal organ precursor comprising a carrier device as defined in claim 1, 2 or 3, and organ cells isolated in pores of the matrix.

5. An artificial internal organ comprising a carrier device as defined in claim 1, 2 or 3, and an organ cell growth structure extending throughout the pores of the matrix.

6. A method of producing a carrier device for an artificial internal organ comprising:

forming a shaped, pressed article simulating an artificial internal organ, of nickel and titanium powders and nickel titanium alloy powder,

subjecting said pressed article to a self-propagating high temperature synthesis to produce nickel titanium alloy from said nickel and titanium powders with formation of a porous matrix corresponding to said shaped article, said porous matrix having a porosity effective to isolate organ cells in the matrix from immune system entities.

7. A method according to claim 6, wherein at least 30% of the porosity of said matrix is defined by pores having a pore size of less than 100 microns.

8. A method according to claim 6 or 7, wherein said shaped, pressed article is formed from a powder composition composed of 45 to 55%, by weight of nickel powder and 55 to 45%, by weight titanium powder, to a total of 100%; and titanium nickel alloy powder in an amount of 5 to 30%, by weight, based on the total weight of nickel and titanium powders.

9. A method according to claim 8, wherein said powder composition contains 47 to 53%, by weight of said nickel powder and 53 to 47%, by weight of said titanium powder to a total of 100%.

10. A method of forming an artificial internal organ comprising: implanting a precursor as defined in claim 4, in a recipient in need of an artificial internal organ, said cells being cells which form the needed organ, and allowing cell growth to establish throughout the matrix.

11. Use of a carrier device as defined in claim 1, 2 or 3, for the formation of an artificial internal organ.

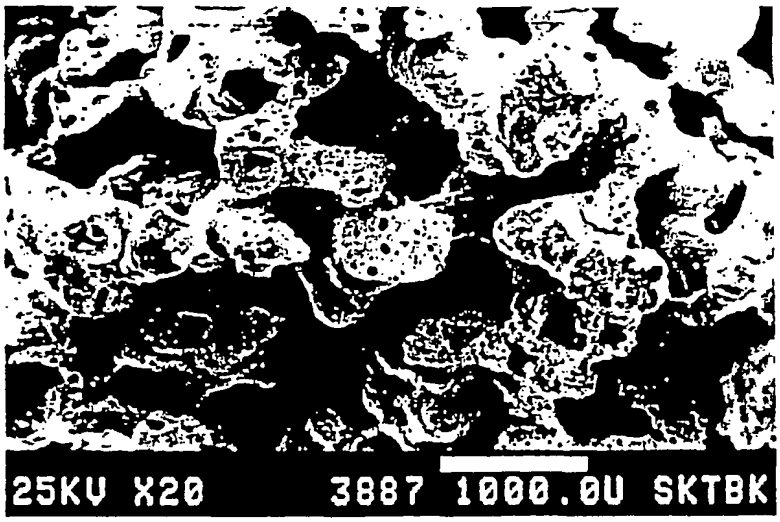

Fig. 1

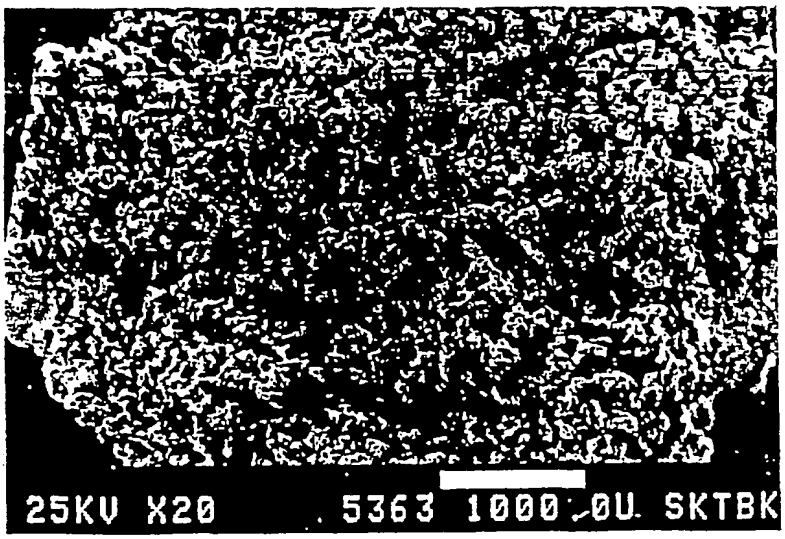

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00711

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/38 A61L27/06 B22F3/23 C22C1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L B22F A61K C22C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, INSPEC, COMPENDEX, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RU 2 143 867 C (DAMBAEV GEORGIJ TSYRENOVICH;GJUNTER VIKTOR EHDUARDOVICH; JASENCHUK JUR) 10 January 2000 (2000-01-10) abstract	1,4-7, 10,11
X	WO 99 34845 A (BIORTHEX INC ;GJUNTER VICTOR (RU); NOVOSIB RESEARCH I OF TRAUMATO) 15 July 1999 (1999-07-15) page 3, line 9 - line 26 page 6, line 24 -page 7, line 15	1,3-5, 10,11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2001	08/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menidjel, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00711

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 198004 Derwent Publications Ltd., London, GB; Class M22, AN 1980-07030C XP002180801 & SU 662 270 A (ITIN V I), 15 May 1979 (1979-05-15) abstract	1,3
P,X	WO 01 13969 A (BIO SMART LTD ;KIM JI SOON (KR); HAN KI SUK (KR); KANG SEUNG BAIK) 1 March 2001 (2001-03-01) page 3, line 5 -page 4, line 15 page 5, line 5 - line 23 page 11, line 9 - line 22	1,3,5,11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 10,11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/CA 01/00711

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
RU 2143867	C	10-01-2000	RU	2143867 C1	10-01-2000
WO 9934845	A	15-07-1999	US	5986169 A	16-11-1999
			AU	1865999 A	26-07-1999
			WO	9934845 A1	15-07-1999
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SU 662270	A	15-05-1979	SU	662270 A1	15-05-1979
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			WO	0113969 A1	01-03-2001